



# Anaemia, Dysfunctional Mitochondria and Heart Failure: Are we Able to Connect These Foes by Understanding Their Pathophysiology?



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## Opinion

Despite major advances in the cardiovascular medicine in the 20th century, heart failure (HF) is an exceptional with estimated prevalence of >37.7 million globally caused by secondary aetiologies ultimately affecting their quality of life, including dyspnoea, poor exercise tolerance, fatigue, and fluid retention. Currently, angiotensin receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, mineralocorticoid receptor antagonists,  $\beta$  blockers, angiotensin receptor blocker neprilysin inhibitors (ARNIs) and advanced device therapies have been administered to patients with reduced ejection fraction (EF) [1].

In general, key features of metabolic adaptations to hypoxia include the ability to maintain cellular [ATP] throughout the hypoxic period, ability to reversibly suppress oxygen consumption under oxygen limiting conditions, and the ability to maintain a stable mitochondrial membrane potential under hypoxia. Precisely, hypoxia diminishes production of ATP by down regulating the activity of electron transport chain through activation of transcription factor hypoxia inducible factor-1 (HIF-1). Also, hypoxia diminishes NADH supply to electron transport chain (ETC) through HIF-1 [2]. When administered orally, HIF stabilizers induce production of erythropoietin to meet organ requirements in ATP production which is otherwise down regulated by HIFs. HIFs also leads to down production of erythropoietin and administering its stabilizers orally induce production to meet organ requirements in ATP production. However, HIF stabilizers affect many other biological processes i.e. glucose and fatty acid metabolism and angiogenesis, so caution should be taken before taking consideration of clinical beneficial [3]. Amongst all disorders caused by depletion of oxygen, myocardial infarction, stroke and cancer are more prevalent. In evolution of humans, systems have developed to ensure optimal oxygenation of all vertebrae species. Lack of oxygen supply results in hypoxia which sensitizes specialized chemoreceptor cells that manage cardiovascular and ventilator rates. Above mentioned

factors collectively lead to production of hypoxia inducible factors (HIFs) and drugs stabilizing these factors are most promising now [3].

Cardiac muscles require the continuous supply of oxygen for its normal functioning to meet different organ needs. In HF, organ systems receive varying degrees of inadequate supply of nutrients and oxygen, causing alterations in neurohormonal pathway and inflammation that leads to anaemia (37%) and iron deficiency (50%). The major pathological factor involved in causing anaemia in HF is intrinsic bone marrow defects, renal failure leads to decreased/reduced production of erythropoietin and nutritional deficiencies such as iron deficiency. In general, patients with chronic kidney disease (CKD), higher age, diabetes mellitus (DM) and other chronic health related diseases are at the highest risk of anaemia. Moreover, increased activation of renin angiotensin system results in fluid and salt retention leading to pseudo-anaemia [3].

Heart failure is mainly caused by insufficient production of energy (ATP) required for normal functioning of cardiac muscle and it is reduced by hypoxia, diminished erythropoietin synthesis i.e. anaemia. Presently one third of HF patients are suffering from anaemia. In a nutshell, it can be corroborated that, anaemia may cause induction of HIFs and dysfunction of mitochondria which results in decreased production of ATP. Hence, connecting these pathophysiological events can be a future target for the treatment of HF.

## References

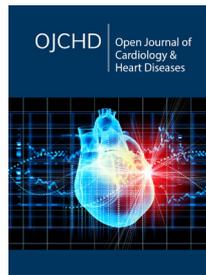
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